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Review Article

Intraocular Pressure Fluctuation: Is It Important?

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Abstract

Elevated intraocular pressure (IOP) is a major risk factor for the development and progression of glaucoma. Previous prospective, randomized, long-term studies have demonstrated the strength of IOP reduction in slowing the progression of disease. It is well known that IOP is not a fixed value but fluctuates considerably over time. Although there have been some studies on IOP fluctuation and the progression of glaucoma, whether IOP fluctuation is an independent risk factor for glaucomatous damage and disease progression remains controversial. In this article, we reviewed the definition of IOP fluctuation, and both the evidence and the speculation for and against the effect of IOP fluctuation on glaucoma progression. Although conclusions seem to vary from study to study, we considered that different studies examined different groups of patients, at different stages of disease, and at different IOP levels. Our conclusion is that these apparently disparate results are not conflicting, but rather can be viewed as complementary. In clinical care, we recommend the consideration of IOP "modulation" rather than just IOP "reduction" when glaucoma patients are treated. Quality-based IOP control may be more effective than quantity-based IOP reduction to prevent or retard disease progression.

Keywords: Intraocular Pressure; Fluctuation; Review

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INTRODUCTION

Elevated intraocular pressure (IOP) is a major risk factor for the development and progression of glaucoma.[1–3] Therefore, IOP measurements provide important information to clinicians about glaucoma diagnosis, assessing the possibility of progression, and monitoring the clinical response to therapy.

It is well known that intraocular pressure is not a fixed value but fluctuates over time. Although there have been a number of studies on IOP fluctuation and the progression of glaucoma, whether IOP fluctuation is an independent risk factor for glaucomatous damage and disease progression remains controversial. Here, we will review the definition of IOP fluctuation, the evidence for and against the effect of IOP fluctuation on glaucoma progression, and what we should consider when we manage glaucoma patients in clinical practice.

IOP fluctuation can be categorized according to the period of time over which the IOP is monitored.

1. Instantaneous IOP fluctuation is defined as the IOP variation that occurs over a very short time period of time (seconds), and is caused by saccades, blinks, eye rubbing, etc.;
2. Diurnal-nocturnal IOP fluctuation, or nyctohemeral fluctuation, refers to IOP variation that occurs over

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the course of a day. The diurnal IOP changes may be partly explained by bodily postural changes associated with blood pressure and episcleral venous pressure changes, diurnal fluctuations in cortisol levels, variations in aqueous production, environmental light and dark cycles, and perhaps seasonal influences.[4–9] This type of IOP fluctuation is also often referred to as central, or humoral IOP fluctuation;

3. Short-term IOP fluctuation is defined as the IOP fluctuation that occurs over days to weeks; and
4. Long-term IOP fluctuation is defined as that which occurs over months to years. A measure of long-term fluctuation can be obtained from repeated IOP measurements that occur during serial office visits.

There have been a number of investigations into the effect of IOP fluctuation on glaucoma progression. Here we will review both the evidence and speculation on the effect of each kind of IOP fluctuation on glaucoma progression.

Instantaneous IOP Fluctuation

There is no direct evidence that instantaneous fluctuation has an effect on glaucoma progression. Animal experiments in primates have demonstrated brief high IOP spikes during saccades, blinks, and eye rubbing.[10,11] Other studies in animal models have shown that acute (though not necessarily instantaneous) IOP elevation can cause structural deformations of the optic nerve head or induce electrophysiologically measured functional changes.[12–15] Based on these animal studies, one may speculate that there are possible effects of transient, but high IOP peaks in susceptible eyes that undergo high strain associated with the stress of IOP spikes.

Diurnal-nocturnal IOP Fluctuation

There have been several reports on the effect of diurnal-nocturnal fluctuation on glaucoma progression.[16–19] Recently, De Moraes et al evaluated the relationship between a 24-hour recording of IOP-related measurements and the rate of visual field progression in treated glaucomatous eyes.[20] In this study, IOPs of forty treated glaucomatous patients were monitored with twenty-four hour recordings using a contact lens sensor (CLS). They found that the number of large peaks (the number of peaks with a height of 90 mV or more) and the mean peak ratio (defined as the mean peak height to time-to-peak, which considers not only the magnitude of the peak, but also how fast it occurred) were the best predictors of faster glaucomatous progression. The results of this study suggest that a combination of CLS parameters obtained during a single 24-hour session provides a signature that seems to explain the rate of glaucoma progression better than a summary of office-hour IOP measurements over multiple visits.

Although it is well known that the highest IOP values usually occur at night, there may also be reasons why nocturnal changes of IOP may not affect the health of the optic nerve. Higher nocturnal IOP in humans is largely due to a supine sleeping position, and increased perfusion in the supine position may counteract IOP elevation. Increased cerebrospinal fluid (CSF) pressure in the supine position may also counteract the stress caused by IOP elevation by reducing the trans-laminar pressure gradient. It is likely that other homeostatic mechanisms exist to compensate for regular biorhythms, such as those that occur with IOP and blood pressure.

Considering these possibilities, we may speculate that, although there is no evidence on the topic, diurnal or nocturnal IOP changes combined with alterations of systemic blood pressure and ocular blood flow may play a role in the pathogenesis of glaucoma. Thus, IOP fluctuations combined with an autoregulatory deficiency of ocular blood flow might damage tissues that are vulnerable to ocular perfusion pressure changes.[21]

Short-term IOP Fluctuation

Short-term IOP fluctuation occurs over days to weeks. There is no evidence that short-term fluctuation has a direct effect on glaucoma progression. However, this type of fluctuation may still be important, since short-term fluctuation may predict long-term fluctuation.

A study performed by Japanese researchers evaluated the relationship between short-term IOP fluctuation (24-hour fluctuation) measured by the Triggerfish® contact lens sensor (CLS; Sensimed AG, Lausanne, Switzerland) and long-term IOP fluctuation measured during office visits over a mean follow-up period of 5 years. They measured four parameters for determining long-term IOP fluctuation:[22] 1) the mean IOP (mmHg) determined during follow-up; 2) the IOP difference, which was defined as the difference between the maximum IOP and the minimum IOP; 3) the standard deviation of IOP; and 4) the peak IOP, which was defined as the maximum IOP. In this study, short-term IOP fluctuation measured with the CLS was significantly correlated with long-term IOP fluctuation [Figure 1]. The authors concluded that the examination of 24-hour IOP fluctuation with the CLS might be useful for predicting long-term IOP fluctuation.

Long-term IOP Fluctuation

Long-term IOP fluctuation, which can be estimated from inter-visit IOP measurements, was concluded to be a risk factor for glaucoma progression by a number of clinical trials. In the Advanced Glaucoma Intervention Study (AGIS), IOP fluctuation was an independent and stronger predictor than mean IOP for visual field (VF)

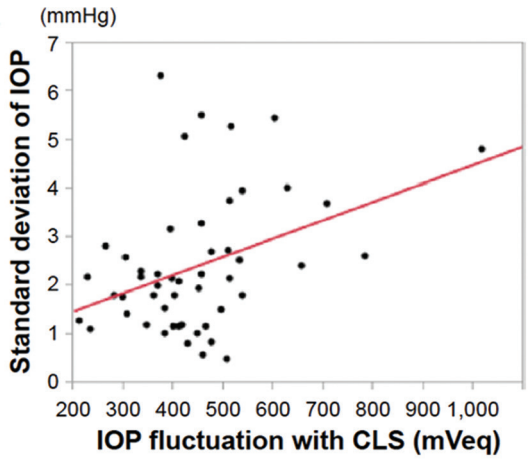

Figure 1. The correlation between short-term (IOP fluctuation with CLS) and long-term IOP fluctuation (standard deviation of IOP). The Spearman correlation coefficient was 0.3272, P = 0.0061. IOP: intraocular pressure; CLS: contact lens sensor. (From Tojo et al, Clin Ophthalmol 2016).

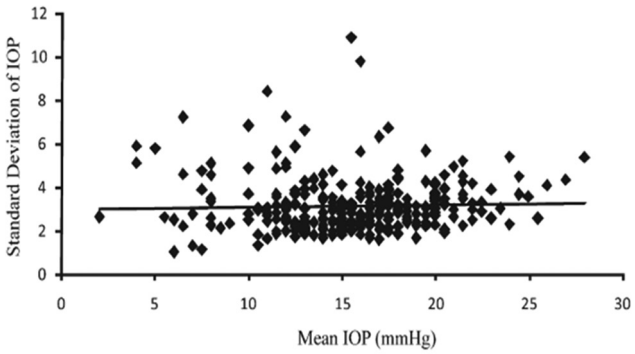

Figure 2. Scattergram showing the relationship between intraocular pressure (IOP) fluctuation (standard deviation of IOP measurements) and mean IOP. There was a weak but statistically significant correlation observed (Spearman r^2 = 0.025, P = 0.006). Long-term IOP fluctuation is associated with VF progression in patients with low mean IOP (area shaded in color), but not in patients with high mean IOP. IOP: intraocular pressure. (From Caprioli et al, Ophthalmology 2008).

progression, and the association of IOP fluctuation with progression was the strongest in eyes with low mean IOPs.[23,24] According to a study published in 2008, we found that the association of IOP fluctuation with progression was the strongest in eyes with low mean IOPs. In this AGIS subset population, there was a very weak correlation between the mean IOP and IOP fluctuation (R^2 = 2.5%) [Figure 2]. When we categorized study participants according to their mean IO*P* values, IOP fluctuation was significantly associated with VF progression in the low mean IOP group (lower tercile group, mean IOP = 10.8 ± 2.5 mmHg), but not in the high mean IOP group (upper tercile group, mean IOP = 20.6 ± 4.5 mmHg, P = 0.2).

The Collaborative Initial Glaucoma Treatment Study (CIGTS) also showed that peak, SD, and range of IOP were all significant factors for 3 dB or more mean deviation (MD) loss, but that mean IOP failed to reveal a significant correlation with VF progression [Figure 3].[25,26]

Other evidence for the association between long-term IOP fluctuation and VF progression is from the Japanese Archive of Multicentral Databases in Glaucoma (JAMDIG) study.[27] In this study, the mean total deviation (mTD) of the 52 test points in the 24-2 HFA VF was calculated, and the relationship between mTD progression rate and seven clinical variables (age, mTD of baseline VF, average IOP, standard deviation (SD) of IOP, previous argon/selective laser trabeculoplasty (ALT/SLT), previous trabeculectomy, and previous trabeculectomy) was analyzed. There was no significant relationship between mean total deviation (mTD of VF) progression rate and mean IOP (P = 0.32, linear mixed model), whereas there was a significant relationship between the mTD progression rate and SD of IOP (P = 0.011, linear mixed model) [Figure 4].

Other reports have also implicated IOP fluctuation as an important risk factor in glaucoma progression.[28–31] A study by Hong et al addressed the question of long-term IOP fluctuation.[29] In this study, a group of patients with IOPs consistently below 18 mmHg after a triple procedure (phacoemulsification, posterior chamber intraocular lens implantation, and trabeculectomy with mitomycin C) was evaluated for VF progression. Patients were divided into 2 groups: those with lower long-term IOP fluctuation (SD ≤ 2 mmHg) and those with higher long-term IOP fluctuation (SD > 2 mmHg). Though mean IOP and the number of glaucoma medications was equivalent in the 2 groups, the group with the lower IOP fluctuation demonstrated significantly better VF preservation.

However, not all studies have shown a positive association between disease progression and IOP fluctuation. Previous studies such as the Ocular Hypertension Treatment Study (OHTS), Early Manifest Glaucoma Treatment (EMGT), European Glaucoma Prevention Study (EGPS), Ocular Hypertension Treatment (OHT) in Diagnostic Innovations in Glaucoma Study (DIGS) found no influence of IOP fluctuation on VF progression.[32–35] The Early Manifest Glaucoma Treatment (EMGT) trial confirmed the strong effect of mean IOP on progression but found no evidence that IOP fluctuation was an independent risk factor for progression. Similarly, the OHTS did not report an independent relationship between IOP fluctuation and the development of glaucoma.

How can these different conclusions about the association of long-term IOP fluctuation and glaucoma progression be explained? We need to consider the similarities of studies that failed to reveal significant correlations between IOP fluctuation and glaucoma progression. In those studies, participants had higher

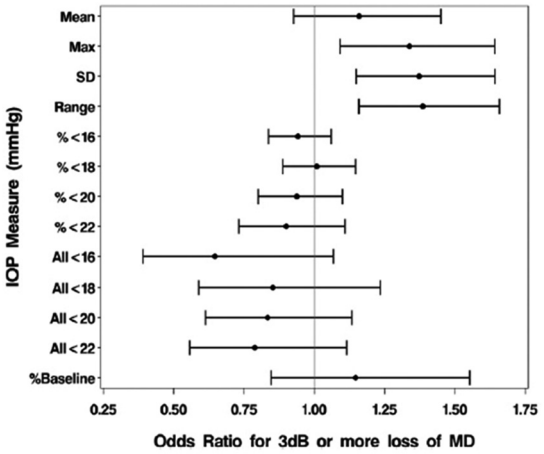

Figure 3. Forest plot of odd ratios (ORs) and 95% confidence intervals (CIs) for the association of individual IOP summary measures with a worsening of mean deviation (≥3 dB decrease) from baseline. IOP: intraocular pressure; MD: mean deviation. (From Musch et al Ophthalmology 2011).

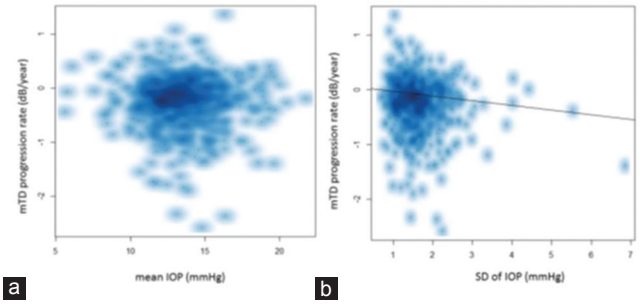

Figure 4. (a) The relationship between the mTD progression rate and mean IOP. There was no significant relationship between the mTD progression rate and mean IOP (P = 0.32, linear mixed model). (b) The relationship between the mTD progression rate and SD of IOP. There was a significant relationship between the mTD progression rate and SD of IOP (P = 0.011, linear mixed model). IOP: intraocular pressure; mTD: mean total deviation; SD: standard deviation. (From Fujino et al Invest Ophthalmol Vis Sci 2016).

but stable IOPs, earlier glaucoma damage, and received relatively modest or no treatment compared to studies like AGIS or CIGTS. Treated patients in the EMGT had limited standardized treatment and did not have incisional surgery, and consequently had higher mean IOPs (16 mmHg). Treated OHTS patients had a mean IOP (19 mmHg) considerably higher than that in the AGIS (14-15 mmHg, depending on race and treatment sequence, and 10.8 mmHg in the AGIS lower mean IOP tercile group) or than that in the study by Hong et al (10 mmHg). We hypothesize that greater IOP fluctuation is damaging in eyes with low mean IOPs (as in Hong et al, the AGIS, and the CIGTS), but when the mean IOP is higher, the role of IOP fluctuation becomes less important (as in the EMGT and the OHTS). Moreover, in the EMGT or OHTS, there existed strong correlations between the mean IOP and IOP fluctuation. Patients with the highest IOPs had the highest IOP fluctuation, whereas patients with low IOPs had the lowest IOP fluctuations. This correlation might mask the effect of IOP fluctuation on glaucoma progression. The AGIS population contained patients with moderate to advanced glaucomatous VF loss who had laser trabeculoplasty or trabeculectomy because maximal tolerated medical treatment failed to control their disease. Different studies have examined different groups of patients, at varying stages of disease, and at different mean IOP levels. Conclusions based on a single population may not be generalizable to other, more heterogeneous groups of patients. Considering these study population differences, we do not believe these findings to be contradictory, but rather complementary.

Why can IOP fluctuation be damaging? Physiologic IOP variation occurs in regular rhythmic cycles. Regular IOP peaks and valleys are normal, and compensatory mechanisms are in place to preserve the integrity of the tissue and the organism. If this "steady state" is disturbed by irregular elevations of IOP, or if normal compensatory mechanisms are faulty, damage may be more likely to occur. Long-term variability may disrupt homeostatic mechanisms. Irregular and large IOP fluctuations may cause loading and unloading of stresses, and as opposed to conditions of static stress, the tissue is unable to compensate and damage occurs. It is also possible that periodic excursions into IOP levels that are damaging might occur, even though the IOP level measured during office visits seems nominal.

Relevance

In the clinical care of glaucoma patients, we should consider IOP "modulation" rather than simply IOP "reduction". Quality-based IOP control may be more important than quantity-based IOP reduction to more effectively prevent disease progression. In cases of progressing primary open angle glaucoma (POAG) in clinical practice, not only a low IOP but also a constant (stable) IOP may be important to control the disease. Sustaining a constant IOP while reducing peaks may be as important as a low IOP in terms of disease progression, especially in patients who progress at low mean IOPs.

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Conflicts of Interest

There are no conflicts of interest.

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